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NDA: 19-955

SUBMISSION DATE: 03/13/92, 09/15/92, 12/03/92, 01/14/93, 01/22/93, 02/19/93

Desmopressin Acetate
0.1 and 0.2 mg Tablets

BRAND NAME: DDAVP

SPONSOR: Rhône-Poulenc Rorer

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: NDA For A New Dosage Form and Route of Administration

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TITLE: "Review of Two Pharmacokinetic Studies in a new NDA"

SYNOPSIS:

Previously, DDAVP intranasal (IN) Rhinal Tube and Nasal Spray (Rhône-Poulenc Rorer Pharmaceuticals) were approved under NDA 17-922 by the Agency for treating Central (cranial) Diabetes Insipidus (CDI) an and DDAVP intravenous (IV) Injection was approved under NDA 18-938 for treating hemophilia A and CDI. However, for NDAs 17-922 and 18-938, they were not reviewed by the Division of Biopharmaceutics (DB) prior to their approval.

The original submission for a new to be marketed DDAVP oral tablet dosage form was filed under NDA 19-955 on 02/06/89 by Rhône-Poulenc Rorer Pharmaceuticals. The firm wanted approval for 0.1 and 0.2 mg tablet strengths. The new tablets are to be indicated similarly for treating CDI and the proposed usual dosage range is 0.1 to 0.2 mg, t.i.d. but doses up to 0.4 mg can be given t.i.d. depending on titration needs.

The submission (NDA 19-955) was, however, withdrawn on 12/26/89 because information/data at one of the pivotal study sites was "not available for audit". At that time the bioreview had been completed (dated 12/12/89) and an FDA letter was communicated to the firm on 01/11/90. In the FDA letter, there were 6 comments regarding the biopharmaceutics (Bio) portion of the submission. In addition, there were 2 comments regarding the dissolution test results that were submitted on 05/10 and 09/11/89. A meeting was held on 01/26/90 between the firm and the Agency to follow up on the Bio comments. A further discussion was held on 04/19/90 to discuss the studies that would be needed to fulfil the NDA Bio requirements. In the meeting two protocols for additional biostudies were presented by the firm and the Agency felt that the proposed protocols seemed to be reasonable for meeting the Bio requirements. However, according to DB's drug review file, one of the protocols (No. RG 84063-101) was submitted to the Agency on 07/16/90 but it was not formally reviewed by DB (dated 08/23/90) since the study had been initiated at that time, and for the other

2004P-0068

REF 1

protocol (No. RG 84063-102), however, there is no record of ever receiving the protocol for review.

Note: The firm indicated (01/26/90) that the new to be marketed tablet formulations were different from the old formulations used in the clinical studies and that the old formulations needed to be changed because there were problems trying to make full-scale production batches. In the follow-up meeting dated 04/19/90 between Rhône-Poulenc Rorer, HFD-510, and DB, DB raised a concern of the lack of demonstration of bioequivalency between the old clinically tested tablet formulations and the new to be marketed formulations. HFD-510 indicated that there was no need for the demonstration of bioequivalency between the clinical and the to be marketed tablet formulations because the safety and efficacy of DDAVP has already been established. Therefore, HFD-510 indicated that only a description of bioavailability of the to be marketed product in addition to the previously submitted clinical studies would satisfy the need for clinical data for approval of this application.

Submitted for review on 03/13/92 were the firm's responses to two Agency comments on dissolution and the results of the two pivotal biostudies entitled "An Open-Label Pharmacokinetic Comparison of Desmopressin Acetate Administered by Oral and Intranasal Routes" [A dose proportionality study; Study 1, protocol No. RG 84063-101] and "An Open-Label Pharmacokinetic Comparison of Desmopressin Acetate Administered by Oral and Intravenous Routes" [A formulation uniformity study; Study 2, protocol No. RG 84063-102].

Study 1 used 36 normal healthy male volunteers and this was a multiple-dose, 4-way crossover, balanced, randomized, Latin square study design with a washout period of 4.67 days. Oral t.i.d. doses of 0.1 mg (Treatment C), 0.2 mg (Treatment A), and 0.4 mg (Treatment D) plus IN t.i.d. doses of 0.01 mg (by rhinal tube, Treatment B) were given up to the 8th dose at which the firm assumed that the steady state had been achieved. The pharmacodynamic (PD) data, e.g., increase of urine osmolality and decrease of urine output from baseline, were obtained from the water-loaded volunteers during the 6th dose (on the 3rd day at 1500) and the pharmacokinetic (PK) data, e.g., plasma DDAVP levels, AUC (area under the plasma concentration-time curve), C_{max} (peak plasma concentration), and T_{max} (peak time to reach C_{max}), etc. were obtained from the 8th dose (on the 4th day at 700) during which the volunteers were not water-loaded. A PK/PD analysis was only conducted for the 0.4 mg dosing regimen (Treatment D).

Note: On 12/21/92, 01/08/93 and 02/03/93, DB recommended that PK/PD analyses be performed for the 0.1 and 0.2 mg dosing regimens by the firm. The firm indicated on 02/19/93 that it did not analyze PK/PD relationships for the 0.1 and 0.2 mg doses and, therefore, no analyses have been forthcoming.

In Study 2, a single dose of 1 x 0.2 mg tablet (Treatment B), 2 x 0.1 mg tablets (Treatment C), or 0.002 mg IV (Treatment A) was given to 36 healthy male volunteers in a balanced, randomized, 3-way crossover study design with a washout period of 2 days. Similar PK parameters were calculated but no PD data were obtained.

The firm provided mean PK parameters with statistical analyses based on un- and/or log-transformed data for assessing i) dose-proportionality of 0.1, 0.2 and 0.4 mg (using the to be marketed 0.1 mg tablets), ii) relative bioavailability (F_{rel}) compared to the 0.01 mg IN dose (Study 1), iii) bioequivalence between the two to be marketed tablet strengths of 0.1 and 0.2 mg, and iv) absolute bioavailability (F_{abs}) compared to the IV 0.002 mg dose (Study 2).

The results obtained from the two one-sided tests procedure with 90% confidence intervals (CI) for AUC and C_{max} values showed that i) the oral doses ranging from 0.1 to 0.4 mg, were not exactly dose-proportional using dose normalized data and ii) the 0.1 and 0.2 mg tablet strengths were not bioequivalent. However, when using mean AUC values that were not normalized for dose they suggest that there might be dose proportionality among 0.1, 0.2, and 0.4 mg doses. The intersubject variations were, however, found to be very large for both studies. Based on the mean normalized AUC values, the F_{rel} for the oral doses was calculated to be around 5% compared to the IN route, and the F_{abs} of the two tablet strengths was calculated to be about only 0.15%. The T_{max} ranged from 0.9 to 1.5 hr indicating that the oral absorption of DDAVP tablet could be fairly rapid. The mean $T_{1/2}$ obtained from the IV administration (Study 2) was found to be 2.24 hr which is much larger than that (4 to 15 min) of endogenous vasopressin. According to an unpublished clinical report submitted by the firm, the oral absorption of DDAVP tablet (using old clinically tested formulation), was not affected by food (breakfast) intake 1 hr prior to dosing in a single-dose crossover study using 11 normal volunteers.

For the PK/PD analysis, a plot of the mean urine osmolality increase vs. mean plasma DDAVP concentration following the 0.4 mg oral dose, presents a counterclockwise hysteresis. A time lag exists between the T_{max} (0.9 to 1.5 hr) and the maximal effect of increase in urine osmolality (3 to 4 hr). More information on PD data analyses provided by the firm and carried out by this reviewer, are covered under General Comments of this bioreview. Among the 3 oral doses of DDAVP tablets studied (Study 1), the 0.4 mg dose is seemingly the most pharmacodynamically similar to the 0.01 mg IN dose in water-loaded healthy volunteers. However, large intersubject variation in PD responses was observed for all treatments and therefore, the package insert (PI) indicates that each patient with CDI and should be titrated individually to his/her optimum therapeutic dose. Finally, there was no metabolism study for this drug conducted in man. Since for the two studies described in this submission used a radioimmunoassay (RIA) method, it can not ruled out that there may have been crossreactivity for unknown metabolite(s) with the antiserum used to analyze collected plasma samples.

RECOMMENDATION:

The DB has reviewed the two biostudies of DDAVP that were filed under NDA 19-955 on 03/13/92 and finds them to be acceptable as a result of the PD data that were submitted in conjunction with the PK data which may be somewhat less than accurate due to assay specificity concerns. The reviewing medical officer should review the General Comments (page 14) and the Labelling Comments (page 17). The Labelling Comments and the dissolution method and specification shown below should be sent to the firm. Prior to approval, DB would like to see the Labelling Comments appropriately addressed by the firm.

in NA ltr

Q = in 30 min

3/30/93

Tien-Mien Chen

Tien-Mien Chen, Ph.D.

Pharmacokinetics Evaluation Branch

Biopharm Day 03/30/93 (Drs. Ludden, Fleischer and Hepp and Mr. Hunt)

RD initialed by John Hunt 4/20/93

FT initialed by N. Fleischer, Ph.D. for N. Fleischer 4/20/93

cc: NDA 19-955, HFD-510, HFD-426 (Chen, Fleischer), Chron, Drug, Reviewer, FOI (HFD-19), F.

TABLE OF CONTENTS: Page

Appendix 2 contains additional tables, figures and attachments described in this bioreview, plus more detailed data/information such as assay validation, data analyses (PK, PD, and statistics), and individual subject data as well as the firm's responses to different telecons held between the Agency and the firm. This information is being retained in DB and can be obtained upon request.

I. BACKGROUND:

DDAVP (desmopressin acetate), is a synthetic analog of naturally occurring pituitary nonapeptide antidiuretic hormone (ADH), i.e., 8-L-arginine vasopressin, which affects renal water conservation. In the desmopressin molecule there are two changes made according to the native protein, i.e., deamination of the N-terminal in position 1 and replacement of 8-L-arginine by 8-D-arginine. The firm claims that these modifications result in a decreased vasopressor action and decreased action on visceral smooth muscle relative to the enhanced antidiuretic activity. It is also reported by the firm that DDAVP has a longer duration (longer half-life) and potency of antidiuretic activity but is virtually devoid of other effects of the natural hormone. However, DDAVP is ineffective for the treatment of nephrogenic diabetes insipidus.

In addition to DDAVP Rhinal Tube and Nasal Spray (NDA 17-922) and DDAVP Injection (NDA 18-938), a single-use diagnostic kit of DDAVP (solution for nasal spray; Concentraid) that is intended for testing the renal concentration capacity, was approved under NDA 19-766, but no PK/Bio data were provided (bioreview of 01/25/90).

II. SUMMARY OF BIOAVAILABILITY/PHARMACOKINETICS/PHARMACODYNAMICS:

1. BIOAVAILABILITY/BIOEQUIVALENCE:

a. Absolute/Relative Bioavailabilities:

Note: For DDAVP following oral or IN t.i.d. dosing in the multiple-dose study (Study 1), AUC_{0-8} was calculated using the trapezoidal rule for the last steady-state dosing interval (the 8th dose) and $T_{1/2}$ was calculated from the apparent terminal phase after the last dose. However, most of the drug concentrations dropped below the minimum quantifiable limit (MQL) prior to the 8th hr sampling time. For the single-dose study of DDAVP tablets vs. IV administration (Study 2 which was conducted at a different clinical site), AUC_{0-16} was calculated and used in PK analyses. However, prior to the 16th hr sampling time, most of the drug concentration levels dropped below the MQL.

From Study 1, the F_{rel} values based on the mean values of AUC_{0-8} of the 0.1, 0.2, and 0.4 mg oral doses, were estimated to be 4.6%, 5.6%, and 6.0% , respectively, as compared to the 0.01 mg IN dose. From Study 2, the values of F_{abs} based on the mean values of AUC_{0-16} for the 2 x 0.1 and 1 x 0.2 mg tablets relative to the 0.002 mg IV dose, were 0.13% and 0.16%, respectively. The F_{abs} values for these oral tablet strengths are really small indicating that DDAVP is unstable, highly susceptible to enzymatic degradation in the gastrointestinal tract, highly metabolized due to the first-pass effect and/or is poorly absorbed. The firm reported that DDAVP is somewhat resistant to proteolysis by stomach enzymes because the molecule does exhibit an effect and it is measurable by RIA in the plasma following oral administration.

Note: In light of the extremely low F_{abs} values, the firm was requested on 12/03/92 to provide information on the effect of food on the oral absorption of DDAVP tablets. However, the firm indicated that after a literature search, it could not find any articles. On 01/22/93, the firm submitted a clinical report (not published) regarding the influence of food intake (breakfast; two pieces of toast with butter and cheese, one boiled egg, a glass of milk and a cup of coffee) on the oral absorption of DDAVP 0.1 and 0.2 mg tablets (old clinically tested formulations) in a crossover study using normal volunteers (n = 11) that had been submitted in the original NDA submission (Attachment 1). That report concluded that based on PD data of urine volume decrease and/or urine osmolality increase (no plasma drug profiles provided), breakfast given 1 hr prior to dosing did not affect the oral absorption of DDAVP 0.1 and 0.2 mg tablets.

b. Dose Proportionality Analysis.

Based on the mean values of untransformed normalized (to 0.4 mg dose) $AUC_{0-\infty}$ and C_{max}, the results of two one-sided tests with 90% CI showed (Study 1) that the CI's did not fall within 80 to 120% in all cases as shown below:

Treatment	C (1 x 0.1 mg)	A (2 x 0.1 mg)	D (4 x 0.1 mg)	p value
$AUC_{0-\infty}$ (pg-hr/ml)	14.5[a] (74.9%[c])	35.8 (68.7%)	75.5 (67.4%)	0.0876[b]
normalized[d]	58.0	71.7	75.5	
	Ref	100-147% (p=0.100[e])	107-153% (p=0.036[e])	
		Ref	86-124% (p=0.639)	
F_{rel}[f]	4.3%	5.6%	6.0%	
C_{max} (pg/ml)	16.5 (29.2%)	16.3 (60.3%)	29.5 (63.8%)	0.325
normalized[d]	65.9	32.6	29.5	
	Ref	-19-117% (p=0.216)	-23-112% (p=0.178)	
		Ref	-47-228% (p=0.909)	
T_{max} (hr)	1.48 (175%)	0.88 (36.3%)	0.98 (33.6%)	0.393

[a]. Original values reported before being normalized.
[b]. P value for the comparison of all 4 treatments in the data set by ANOVA.
[c]. Coefficient of Variation (CV) in %.
[d]. Normalized to 0.4 mg dose.
[e]. P value for the contrast from the crossover ANOVA model (**TABLE 1**).
[f]. Compared to the 0.01 mg IN dose
[*]. Statistically significant with $p<0.05$.

Note: No log-transformed data were provided for Study 1, since AUC_{0-8} was found to be "zero" for subject Nos. 13 and 15 after 0.1 mg DDAVP administration.

A graphical representation of the AUC_{0-8} vs. dose is depicted in **Figure 1**. The slope of the regression line is significantly different from zero (P = 0.0001) and the intercept of -5.9 is not significantly different from zero (P = 0.106). However, the firm reported that the linear relationship between AUCs and doses is weak.

The proportionality ratios among the 3 doses were also analyzed by this reviewer and the results are summarized below:

i.

AUC Ratio	Theoretical	Calculated
A/C	2	2.47
D/C	4	5.21
D/A	2	2.11

ii.

C_{max} Ratio	Theoretical	Calculated
A/C	2	0.988
D/C	4	1.79
D/A	2	1.81

These results indicate that oral administration of DDAVP appears to be generally proportional over the dosage range (0.1 to 0.4 mg) according to mean AUC values. The calculation of mean C_{max} for 0.1 mg dose included an outlier # 22 (with a C_{max} of 294.888 pg/ml at T_{max} of 16 hr) as reported by the firm. When excluding the outlier # 22, the mean C_{max} ± SD (n = 35) was 8.52 ± 5.99 pg/ml with a CV of 70.4% and mean T_{max} was 1.06 ± 0.73 hr with a CV of 68.4%. The values of CV% are now close to that of other parameters. Therefore, C_{max} ratios being less than the theoretical ones is most likely due to the outlier # 22.

c. Bioequivalence:

From Study 2, the results of analysis using the two one-sided tests procedure with 90% CI analyses for both untransformed and log-transformed AUC_{0-16} and C_{max} values of the biolots are summarized below:

Treatment	B (1 x 0.2 mg) <Test>	C (2 x 0.1 mg) <Reference>
AUC_{0-16} (pg-hr/ml)	30.5 (104%[a]) **<26.5% ↑>[b]**	24.1 (77%)
i. Untransformed	95-157% **"FAIL"** (p=0.163[c])	Ref
ii. Log-transformed	89-145% **"FAIL"** (p=0.379)	Ref
F_{abs}	0.13%	0.16%
C_{max} (pg/ml)	15.0 (93%) <13.6% ↑>	13.2 (85%)
i. Untransformed	94-133% **"FAIL"** (p=0.252)	Ref
ii. Log-transformed	93-129% **"FAIL"** (p=0.357)	Ref

[a]. CV in %.
[b]. Percent difference in means, i.e., (Test-Reference)/Reference • 100%.
[c]. Not statistical significance with P>0.05.

Note: The firm submitted the above data without inclusion of subject No. 63. The firm claimed that the subject No. 63 is an outlier

(possibly due to a switch/mislabelling for the blood samples collected from the Treatments A and B).

Since the content uniformity for the 0.1 mg tablet biolot was less than that of the 0.2 mg tablet biolot (93.1% vs. 102.3%; a 9.9% difference), this reviewer recommended on 12/03/92 that the firm take into account the difference in content uniformity of the two strengths and reanalyze the above data. However, the firm indicated on 12/09/92 that the results did not change the conclusion of bioinequivalence between the tablet strengths. Therefore, the above results indicate that the 0.1 and 0.2 mg tablet strengths are not bioequivalent based on untransformed or log-transformed data analyses.

2. PHARMACOKINETICS:

The PK parameters were calculated by the noncompartmental method (details in the PK section of Study 1, Appendix 1). The mean (with CV%) PK parameters obtained from Studies 1 and 2 are summarized in **TABLE 2** and mean plasma drug concentration-time data are summarized in **TABLES 3** and **4**. Mean plasma profiles were shown in **FIGURES 2** and **3**.

Large CV% for the mean AUC and C_{max} values (Study 1) indicates that there is a large degree of intersubject variability. The CV% obtained from Study 2 was found to be even larger. T T_{max} values for oral tablets ranged from 0.9 to 1.5 hr with a relatively small CV% and were not statistically different ($p=0.393$, **TABLE 3**). Most of the plasma samples collected for the C_{min} determination had plasma drug concentrations below the MQL of 2.8 pg/ml. Therefore, a valid statistical analysis of C_{min} for assessing steady state was not available. The mean values of $T_{1/2}$ ranging from 1.61 to 1.69 hr. were indeed pretty consistent among oral and IN administrations (Study 1). However, they were smaller than that obtained from IV, 2.24 hr (Study 2, **TABLE 2**).

The firm reported that from Study 2, the $T_{1/2}$ could not be calculated based on the oral administration of 0.2 mg doses (under the same conditions and using the same RIA method as for Study 1). It was found that the $T_{1/2}$ obtained from Study 1, could have been underestimated, i.e., due to the extremely small F_{abs} values and the MQL of the assay method employed. Therefore, the $T_{1/2}$ obtained from Study 1 may not accurately represent the apparent terminal $T_{1/2}$ of this drug after oral and IN administrations.

Lastly, the MQL of the assay method related to the extremely small F_{abs} values probably affects an accurate calculation of AUC for the 0.1 mg dose (Study 1). This would in turn limit an accurate AUC assessment of the drug's dose-proportionality when the higher doses are compared to 0.1 mg dose AUC.

3. METABOLISM:

There was no metabolism study of this drug conducted in man according to firm's responses dated 12/03/93 (Attachment 2).

4. POPULATION:

Studies 1 and 2 were all conducted in normal healthy male volunteers. The demographic information for the volunteers is provided in each study.

5. PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS:

A time lag of around 2 hr was found between the T_{max} of about 1.5 hr and the maximal effect of urine osmolality increase at about 3 to 4 hr. The firm provided the PK/PD analysis of this drug following the administration of the 0.4 mg dose (Treatment D in Study 1) only (**FIGURES 4 and 5**). A plot of the mean urine osmolality increase (during the 6th dose) vs. mean plasma DDAVP concentration for the times from 0 to 6 hr (during the 8th dose), presents a counterclockwise hysteresis (**FIGURE 6**).

6. FORMULATIONS AND DOSAGES USED:

	0.1 mg tablet	0.2 mg tablet
DDAVP (free base)	0.089 mg	0.178 mg
Lactose		
Potato Starch		
Povidone (USP)		
Mg Stearate		

The 0.1 and 0.2 mg tablets did not have the same ratio of active/inactive ingredients, but they had exactly the same amounts of inactive ingredients (Attachment 3). On 03/23/93, the firm was requested to provide the formulation used in the clinical studies and it is included in Appendix 2.

The information on DDAVP dosages used in Studies 1 and 2 is summarized below:

Study 1:

Treatments C, A, and D: 1 x 0.1, 2 x 0.1, and 4 x 0.1 mg, respectively

DDAVP 0.1 mg tablets:	Lot No. 9007179 (Ferring Lot No. QE9229)
Production size batch:	100,000 (20% of full-scale production size)
Content uniformity:	93.1 ± 2.1% (n=10)
Date of manufacture:	05/16/90

Commercial Equipment: Yes
Site of Manufacture: Ferring Pharmaceuticals, Malmo, Swedan

Treatment B: 0.01 mg of DDAVP in 0.1 ml solution through IN rhinal tubes

DDAVP 0.1 mg/ml solution: Lot No. 9003038 (Ferring Lot No. PE8593)
(Currently marketed; 2.5 ml/vial)

Study 2:

Treatment A: 0.002 mg of DDAVP in 0.5 ml solution given by intravenous injection.

DDAVP 0.004 mg/ml solution: Lot No. 9003037 (Ferring Lot No. PK8860)
(Currently marketed, 1 ml/ampule and 10 ml/vial)

Treatments B: 1 x 0.2 mg tablet given orally

DDAVP 0.2 mg tablets: Lot No. 9007180 (Ferring Lot No. QE9230)
Content uniformity: 102.3 ± 2.9% (n = 10)
Production size batch:
Date of manufacture: 05/28/90
Commercial Equipment: Yes
Site of Manufacture: Ferring Pharmaceuticals, Malmo, Sweden

Treatments C: 2 x 0.1 mg tablets given orally

DDAVP 0.1 mg tablets: same Lot No. 9007179 (Ferring Lot No. QE9229)

Notes: 1. According to the firm's response (03/13/92) to an FDA letter dated 01/11/90, the proposed full-sale production size batch will be set at (Attachment 4).

2. The information on content uniformity of the tablet strengths was requested by this reviewer on 11/24/92 and the firm submitted the information on 12/03/92 (Attachment 2).

3. Minirin® is the brand name of desmopressin (DDAVP) for nasal, intravenous and oral products that are currently marketed in

Europe and some other countries. Minirin® has the identical formulations as that to be marketed in the US.

7. DISSOLUTION:

The firm's responses (with dissolution test results) to 2 Agency comments on dissolution (dated 01/11/90), were provided in the submission dated 03/13/92 (Attachment 4). However, the methodology employed was not clearly stated.

Note: Currently there is no USP or FDA dissolution specification available for DDAVP tablet.

From the tables and figures the firm provided using Study 2 biolots (Attachment 4), it was shown that i) DDAVP appeared to be stable in various pH environments (e.g., simulated gastric fluid without enzyme, distilled water, and simulated intestinal fluid without enzyme; from pH 2.86 to 8.28) and ii) the 0.2 mg (whole) tablet had a relatively faster rate and greater extent of dissolution compared to the 0.1 mg (whole) tablet in all media.

Note: Since in the proposed PI, the firm indicates that broken tablets (1/2 of 0.1 mg tablet) can be given as a lower starting dose for pediatric use and that tablet dosage should be increased or decreased (1/2 tablet) as needed to obtain adequate antidiuresis, this reviewer requested dissolution data of broken tablets of both 0.1 and 0.2 mg tablet strengths on 11/02/92. On 01/14/93, the firm submitted the results of dissolution tests of whole and broken 0.1 and 0.2 mg tablets (Attachment 5). It is also summarized in **TABLE 5**.

According to the dissolution test results submitted on 01/14/93 for the same biolots that were previously tested (Attachment 5), the broken 0.1 and 0.2 mg tablets gave similar dissolution profiles (rate and extent) as the whole 0.1 and 0.2 mg tablets, i.e., no apparent difference between whole 0.1 and 0.2 mg tablets, between the broken tablets or between the whole and broken tablets (**TABLE 5**). However, the new dissolution results were somewhat different from the previous data where the whole 0.2 mg tablets had a relatively faster rate and greater extent of dissolution than the whole 0.1 mg tablets (**TABLE 5**). On 02/09/92, this reviewer raised the concerns on the different dissolution profiles obtained from the two tests. The firm submitted its response on 02/19/93 (Attachment 10) and indicated that the difference was due to the use of solid-phase extraction cartridges to collect dissolution samples. However, the firm's explanation was not very convincing.

8. SAMPLE COLLECTION:

Please see blood sample collection and treatment in details in each study in Appendix 1.

9. ASSAY:

Plasma samples were stored up to 247 days. Prior to assay the samples were first precipitated followed by extraction and evaporation procedures. Dried extracts were stored at -20°C until reconstituted prior to assay. The study samples, buffer controls and extraction controls were analyzed in duplicate. The information on assay specification, validation, was provided in the assay section of each study. The detailed assay validation report is located in Appendix 2.

For the two studies, an RIA method was used. However, since no metabolism information was provided, the crossreaction of a metabolite(s), if existing, with the antiserum could potentially occur. Additionally, "non-zero" baseline values (prior to the first dose, i.e., at -56 hr) were found for some of the subjects for all treatments in Study 1.

Note: In a telecon held on 11/24/92, the issue of the "non-zero" baseline values was raised by this reviewer. On 12/02/92, the firm indicated that the samples with non-zero values at baseline had been reassayed and the values were consistent with the previously reported values. The firm believes that the non-zero values at baseline are due to processing error, e.g., mistake and/or contamination but unlikely to be due to crossreaction by a metabolite(s).

10. DATA ANALYSIS:

Please see the data analysis section of each study for detailed PK, statistical, or PD evaluation information. It should be noted that in the analysis of PK/PD relationships (Study 1), the PD data were obtained from the water-loaded volunteers during the 6th dose while the PK data were obtained from volunteers not being water-loaded during the 8th dose. The firm, however, assumed that the inter-/intra-subject variations and the PK profiles obtained for the 6th dose would be similar to that from the 8th dose.

III. GENERAL COMMENTS (Need not to be sent to the firm):

1. On 01/08/93, a telecon was held between DB and the firm where statistical analyses (ANOVA) for the comparisons of PD parameters (Study 1) were requested, e [illegible]urine volume decrease, maximum urine osmolality increase, and AUC o [illegible] osmolality increase from baseline vs. time among the oral

doses and the IN dose. On 01/22/93, the firm submitted a supplement to address the Agency's concerns (Attachment 1).

The firm indicated that for the 0.2 and 0.4 mg oral doses, although the PK data were statistically significantly different, the PD analyses showed that there was only a 10 to 15% difference between the 0.2 and 0.4 mg oral doses and that they are <u>not</u> statistically different from the 0.01 mg IN dose. The firm further indicated that when using the two one-sided t-tests procedure with 90% CI on the PD parameters (Attachment 1), the 0.2 and 0.4 mg doses were all within a range of 80 to 120% of the mean values of the PD parameters obtained from the 0.01 mg IN dose (Attachment 1). Therefore, the 0.4 and 0.2 mg oral tablet doses were considered to be pharmacodynamically equivalent to the 0.01 mg IN dose. The firm, however, emphasized that dosing the patients with CD! should be titrated on an individual basis.

Between 02/17 and 2/19/93, the firm submitted further PD data analyses for the 0.4 mg oral dose and the 0.01 mg IN dose (Attachment 10). Ratio analyses (75/125 rule) of the PD parameters between the 3 oral doses and the IN dose were conducted by this reviewer and the results of the ratio analyses are summarized below:

Ratio Analyses on PD parameters for 3 oral doses vs. IN dose

Dose	Parameters	<0.75	0.75-1.25	>1.25
0.4 mg:				
	Max. Osmolality (mOsm/kg)	2/36[a] (5.6%)[b]	30/36 (83.3%)	4/36 (11.1%)
	AUC of Osmolality (mOsm-hr/kg)	7/36 (19.4%)	19/36 (52.8%)	10/36 (27.8%)
	Total Urine Vol. (ml) ↑	3/36 (8.3%)	27/36 (75%)	6/36 (16.7%)
0.2 mg:				
	Max. Osmolality (mOsm/kg)	9/36 (25%)	24/36 (66.7%)	3/36 (8.3%)
	AUC of Osmolality (mOsm-hr/kg)	16/36 (44.4%)	17/36 (47.2%)	3/36 (8.3%)
	Total Urine Vol. (ml) ↑	10/36 (27.8%)	24/36 (66.7%)	2/36 (5.6%)

0.1 mg:

Max. Osmolality (mOsm/kg)	20/36 (55.6%)	16/36 (44.4%)	0/36 (0%)
AUC of Osmolality (mOsm-hr/kg)	30/36 (83.3%)	4/36 (11.1%)	2/36 (5.6%)
Total Urine Vol. (ml) ↑	13/36 (36.1%)	21/36 (58.3%)	2/36 (5.6%)

[a]. Number of subjects out of total (36 subjects) with ratio values < 0.75, between 0.75 and 1.25, and > 1.25.

[b]. Percent of subjects out of total within ratio categories.

From the above ratio analyses it seems that the oral 0.4 mg dose probably is the closest to the 0.01 mg IN dose based on total urine volume decrease and maximum osmolality increase.

2. In an article published by Williams et al (Attachment 1), the authors concluded that when DDAVP IN solutions (0.1 and 0.2 mg) were given orally to water-loaded normal volunteers (n = 5) and adult patients with CDI (n = 7) a marked antidiuresis and mean urinary osmolality increase in normal volunteers as well as in adult patients with CDI was observed and that the oral DDAVP may be useful for treating some patients with CDI. The reviewing medical officer concurred with the conclusion drawn in this article.

   Studied further and compared by this reviewer were the PD responses reported in the article (by Williams et al; Attachment 1) and in Study 1. The results of the comparisons are summarized in **TABLE 6** and shown in **FIGURE 7**. For a 0.2 mg oral dose, the profiles of mean UFR (urine flow rate in ml/hr) vs. time for both water-loaded normal volunteers and adult patients with CDI reported in the article and the profiles for the water-loaded normal volunteers (n = 36) in Study 1 are comparable. However, 7 adult patients with CDI showed somewhat a lesser change of urine osmolality than that seen in 5 normals. For 0.1 mg oral dose, the water-loaded normal volunteers exhibited similar UFR profiles for DDAVP IN solution (0.1 mg) given orally and for 0.1 mg tablets (**TABLE 6** and **FIGURE 7**). The 0.2 mg dose tended to show a more dramatic drop in UFR and it had a longer duration of action. Therefore, based on the results of the above comparisons, it seems feasible that the dynamic response relationships obtained from the normal volunteers could possibly be extrapolated to adult patients with CDI at least for UFR.

3. Ideally, the firm should have collected PD data in addition to PK data in Study 2 so that PK/PD relationships for both the 2 x 0.1 and 1 x 0.2 mg tablets could have been analyzed in order to better help assess the equivalence issue between the 0.1 and 0.2 mg tablet strengths.

However, since the PD analyses from Study 1 showed that there was only about a 10 to 15% difference in UFR and urine osmolality between a twofold incr[illegible] in dose (0.2 and 0.4 mg) and resulting AUC, the 26.5% difference sa[illegible] JC between the 2 x 0.1 and 1 x 0.2 mg tablets obtained in Study 9) would probably not result in big difference in PD responses. [illegible]re, the statistical bioinequivalence seen between the 0.1 and 0.2 is probably not a concern.

[illegible] nother published article (by Vilhardt and Lundin, Gen. Pharmac. Vol 17, No. 4, 481-483, 1986; Attachment 6) it was concluded from a single-dose study in water loaded normal volunteers (n = 6), that a 0.02 mg (Not 0.01 mg as used in Study 1) IN dose is similar to that of 0.1 and 0.2 mg oral tablets ($p > 0.05$) in terms of maximum urinary osmolality increase. This conclusion is seemingly in contrast to that obtained from Study 1. Under this circumstance as raised in the PI, titrating patients to their needs probably requires close attention/observation by physicians initially when switching the route of administration of DDAVP from IN solution to oral tablet and vice versa.

5. In a third article (by Westgren et al, Archives of Disease in Childhood, Vol. 61, 247-250, 1986; Attachment 7) it was concluded that based on the previously IN dosing experiences in children with CDI (n = 7) and the study in these young patients using oral tablets, a linear correlation was found between the daily IN doses and daily tablet doses (**Figure 8** and Attachment 7) which may provide a better reference/prediction for the maximum PD effects when switching route of administration occurred for children with CDI.

IV. LABELLING COMMENTS (need to be communicated to the firm):

Note: A copy of revised package insert that was submitted on 02/19/93, is provided in Attachment 8.

1. It is recommended that the chemical name and structure of DDAVP, including molecular weight, be provided in the description section of physical and chemical properties of DDAVP at the beginning of the package insert. This change was requested by the reviewing chemist, but it did not appear in the recently revised package insert.

5/10/93 draft

2. The first paragraph in the package insert currently states "DDAVP (desmopressin acetate) is an antidiuretic hormone affecting renal water conservation and is a synthetic analogue of 8-arginine vasopressin.".

Since DDAVP is not an authentic endogenous hormone and since DDAVP has two modifications in its molecular structure as compared to endogenous hormone vasopressin (ADH), it is better to modify the sentence as follows:

"DDAVP (desmopressin acetate) is a synthetic analogue of endogenous 8-arginine vasopressin which affects renal water conservation. DDAVP has two changes in its molecular structure as compared to vasopressin."

3. In the **CLINICAL PHARMACOLOGY** section of the package insert, the following sentences should be added to the end of the 2nd paragraph:

"The bioavailability of DDAVP oral tablets is about 5% compared to intranasal DDAVP, and about 0.15% compared to IV DDAVP. The time to reach maximum plasma DDAVP levels ranges from 0.9 to 1.5 hr following oral or intranasal administration. The onset of antidiuretic effect occurs at around 1 hr and it reaches a maximum at about 3 to 4 hr based on the measurement of urine osmolality increase

4. In the **CLINICAL PHARMACOLOGY** section of the package insert, the following words (underlined) should be added to the 6th paragraph for more complete information as follows:

For the first sentence:

In one study (21), the pharmacodynamic characteristics of DDAVP during an 8-hr dosing interval at steady state after oral.....

For the second sentence:

The dose administered to 36 hydrated (water-loaded) healthy male adult volunteers.....

Also in the 7th paragraph, addition of words (underlined) is recommended as follows:

For the first sentence:

With respective to the mean values of total urine volume decrease and maximum urine osmolality increase from baseline, the 90%....., when compared to the 0.01 mg intranasal dose.

5. Under the subsection of Central Cranial Diabetes Insipidus, in the **PEDIATRIC USE** section, the last paragraph currently states "Treatment with DDAVP Tablets in adequately controlled studies ir
conducted for up to 8 weeks." should be moved to the end of the next section . In addition, it is recommended to provide the dosage range and strength of tablets used in the adequately controlled clinical trials to support the approval of the tablet

dosage form. The above information has been requested by the Agency on 12/03/92.

6. Under the subsection of Central Cranial Diabetes Insipidus, in the **DOSAGE ADMINISTRATION** section, the 10th sentence currently states "Tablet dosage should be increased or decreased (1/2 tablet) as nec[illegible]to obtain adequate antidiuresis.". It is not clear as to whether 1/2 tablet of 0.1 or 0.2 mg is to be given. Therefore, it is recommended that the firm revise the sentence and make it precise and clear.

done in 5/10/93 draft

7. Under the subsection of Central Cranial Diabetes Insipidus, in the **DOSAGE ADMINISTRATION** section, the 12th sentence currently states "During the course of therapy, slight adjustment in dosage may be necessary to compensate for changes in food and water intake." However, it is not clear as to how to slightly adjust the dose and on what basis. According to an unpublished clinical report that was previously submitted, it was concluded that food intake did not affect the oral absorption of DDAVP 0.1 and 0.2 mg tablets.

omitted from 5/10/93 draft

On 04/06/93, the above concern was raised to you (the firm) and on 04/07/93, you notified the Agency that you agreed to d[illegible] the entire sentence.

Study 1

Table 1 Contrasts and 90% Confidence Intervals for Cmax and AUC_{0-8}.

Data Set	Parameter	$P > F^1$	Contrast	$P > F^2$	90% CI

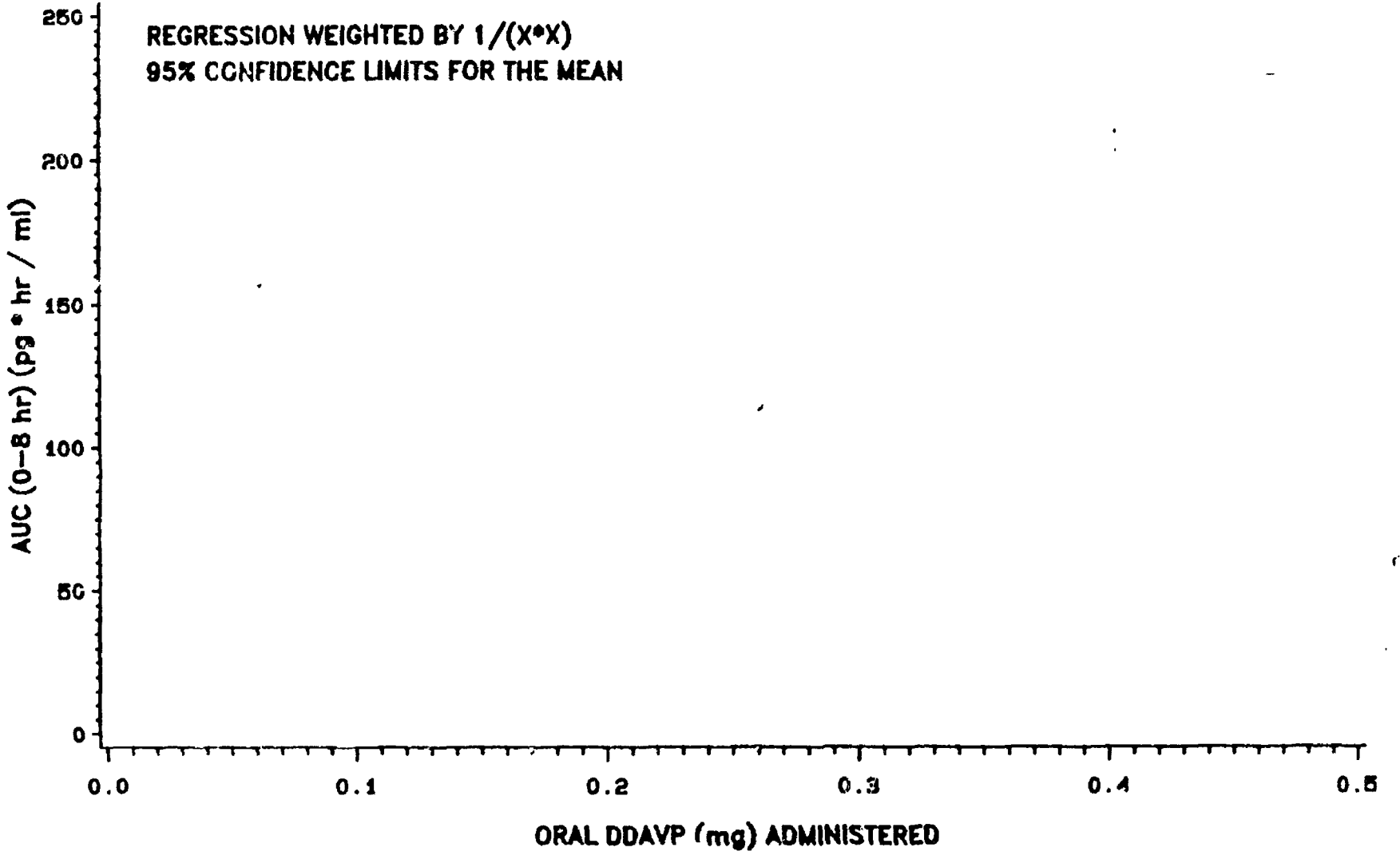
[1] P value for the comparison of all treatments in the data set by analysis of variance.
[2] P value for the contrast from the crossover analysis of variance model.

FIGURE 1.

Study 1

RG 84063-101

DDAVP DOSE PROPORTIONALITY AND ANTIDIURETIC ACTIVITY
LINEAR REGRESSION OF AUC AND DOSE



Rhône-Poulenc Rorer
DDAVP Tablets
NDA #19-955

TABLE 2
IN VIVO STUDY SUMMARY DATA OF DDAVP (mean cv%)

PIVOTAL STUDIES

Study #	Route of Administration Dosage form		Dose (mg)	Cmax (pg/ml)	Tmax (hr)	AUC_{0-8} (pg*hr/ml)	Kel (hr^{-1})	t½ (hr)	F (normalized)
DD-91-50	P.O. Ferring Tablets								
Steady-State	Tx	C	0.1 mg t.i.d.	16.5 (292)	1.48 (175)	14.5 (74.9)	---	---	---
dose proportionality		A	0.2 mg t.i.d.	16.3 (60)	0.88 (36)	35.8 (68.7)	0.43 (49)	1.61	---
(G 84063-101)		D	0.4 mg t.i.d.	29.5 (64)	0.98 (34)	75.5 (67.4)	0.41 (49)	1.69	
study 1	rhinyle tube	B	0.01 mg t.i.d.	17.8 (129)	1.56 (208)	31.6 (66.5)	0.42 (70)	1.65	
DD-91-51	P.O. Ferring Tablets					AUC_{0-16}			
Absolute bioavailability	Tx	C	2 x 0.1 mg	13.2 (85)	1.06 (33)	24.1 (77)	---	---	---
and bioequivalency		B	1 x 0.2 mg	15.0 (93)	1.05 (39)	30.5 (104)	---	---	---
(G 84063-102)	I.v. Inject.	A	0.002 mg	---	---	190.0 (17)	0.31 (20)	2.24	0.16%
study 2									

Study 1

TABLE 3 Mean and Coefficient of Variation for DDAVP Raw Plasma Concentrations (pg/ml) and Derived Pharmacokinetic Parameters on Day 4 for All Four Treatments

Time (hr)	A 0.2 MG P.O.	% CV	B 0.01 MG I.N.	%CV	TREATMENT C 0.1 MG P.O	% CV	D 0.4 MG P.O.	% CV	ANOVA P > F[1]
0.00									
0.33									
0.50									
0.75									
1.0									
1.25									
1.5									
2.0									
3.0									
4.0									
6.0									
8.0									
12.0									
16.0									
AUC(0-8 hr) pgxhr/ml									
Cmax (pg/ml)									
Tmax (hr)									
kel (1/hr)									
$T_{1/2}$ (hr)									

[1] P value for the global ANOVA treatment effect for the three oral tablet treatments and the intranasal treatment (A, B, C, and D).

Study 2

Table 4. Mean and Coefficient of Variation for DDAVP Plasma Concentrations (pg/ml) and Derived Pharmacokinetic Parameters (excluding subject 63).

	A		B		C		
Time/ Parameter	0.002 mg IV Mean	CV(%)	0.2 mg Tablet Mean	CV(%)	0.1 mg Tablet x 2 Mean	CV(%)	ANOVA P > F[1]
0.00							
0.08							
0.17							
0.25							
0.33							
0.50							
0.75							
1.00							
1.25							
1.50							
2.00							
3.00							
4.00							
6.00							
8.00							
12.0							
16.0							
AUC(0-16 hr)[2]							
Cmax[3]							
Tmax (hr)							
kel (1/hr)							
$T_{½}$							

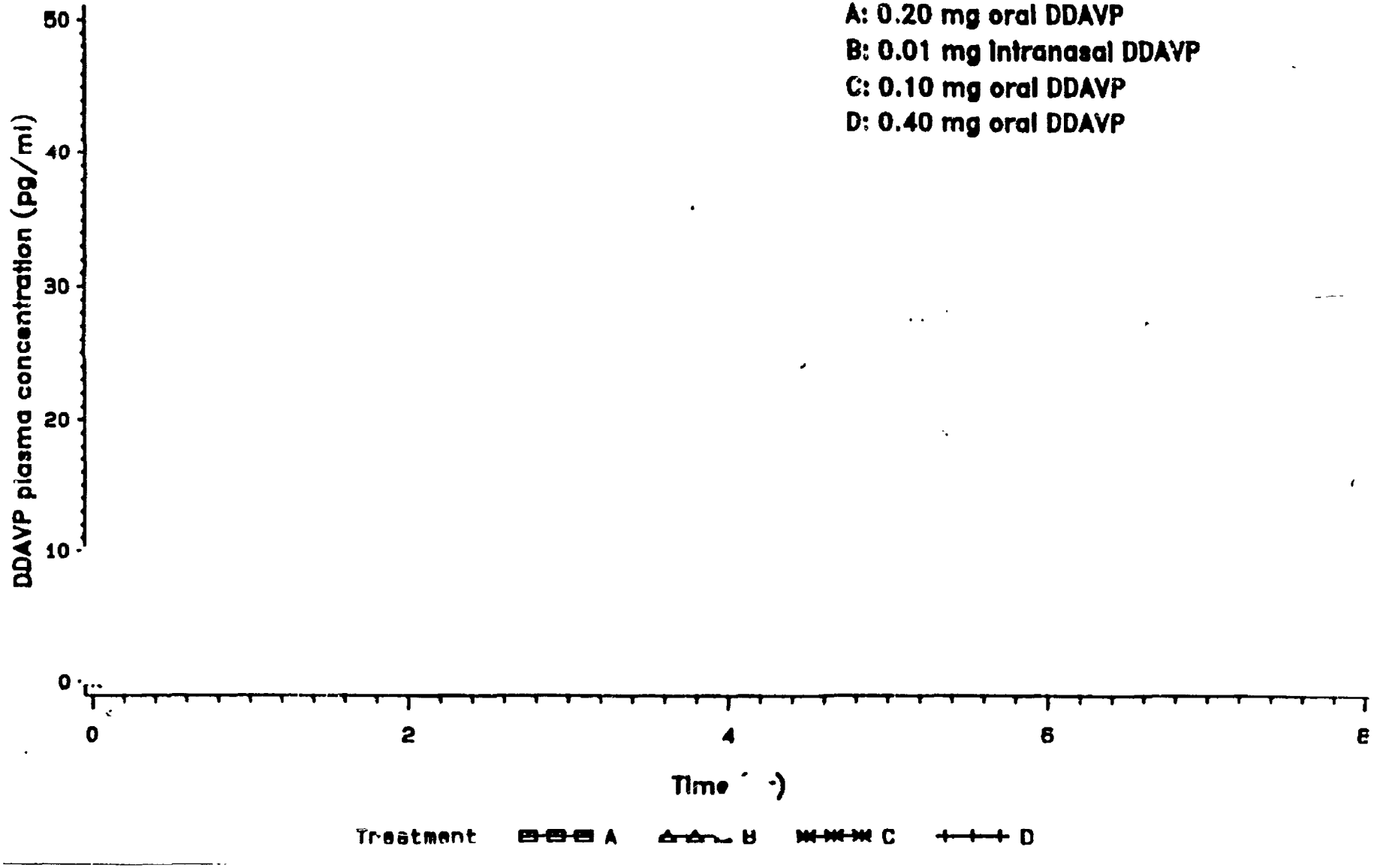
[1] Comparison of 0.2 mg tablet to the 0.1 mg tablet x 2
[2] (pg*hr/ml)
[3] (pg/ml)

FIGURE 2.

Study 1

RG 84063-101

DDAVP DOSE PROPORTIONALITY AND ANTIDIURETIC ACTIVITY
MEAN DDAVP CONCENTRATION VERSUS TIME



study 2

FIGURE 3.

RG 84063-102

DDAVP TABLETS: A FORMULATION UNIFORMITY STUDY
MEAN DDAVP CONCENTRATION VERSUS TIME

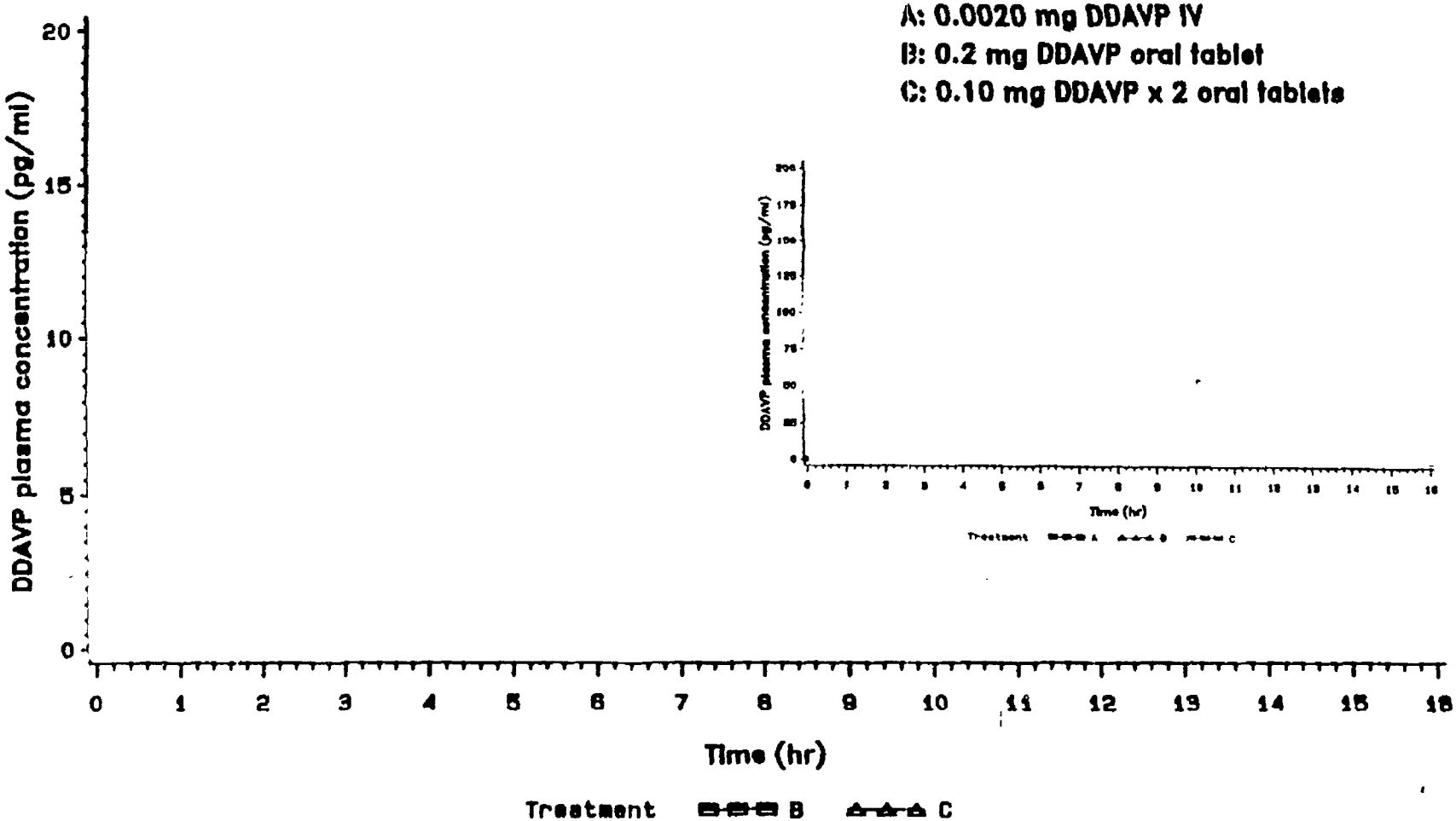


FIGURE 4

Study 1

RG 84063-101

DDAVP DOSE PROPORTIONALITY AND ANTIDIURETIC ACTIVITY
MEAN URINE VOLUME VERSUS TIME

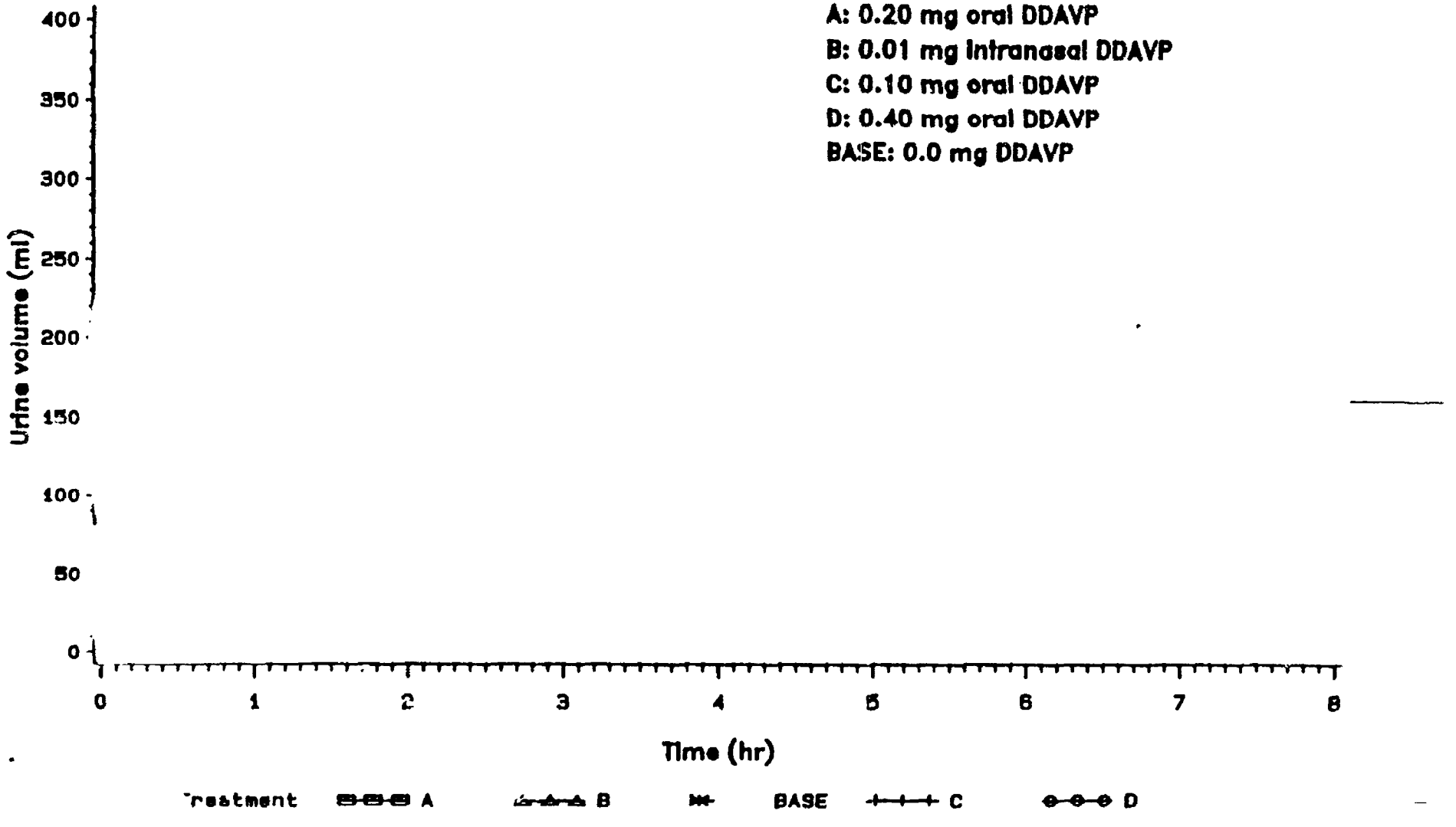


FIGURE 5

Study 1

RG 84063–101

DDAVP DOSE PROPORTIONALITY AND ANTIDIURETIC ACTIVITY
MEAN URINE OSMOLALITY VERSUS TIME

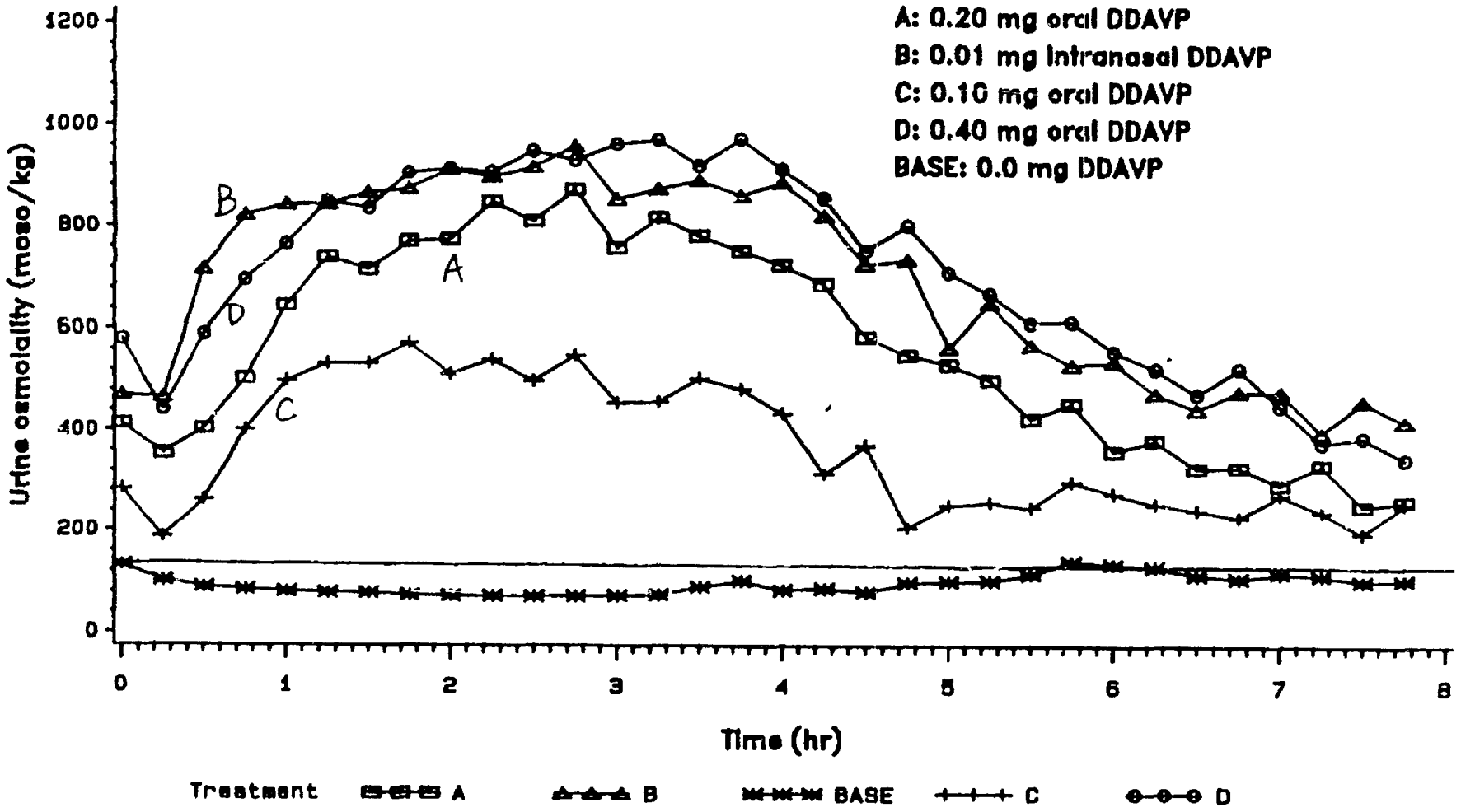


TABLE 5 Dissolution Tests for 0.1 and 0.2 mg DDAVP Tablets

Media: Distilled Water	(03/13/92) w/o enzyme		w/o enzyme		(01/14/93) Distilled Water			
Time (min)	0.2 mg[a] (Whole)	0.1 mg (Whole)	0.2 mg (Whole)	0.1 mg (Whole)	0.2 mg (Whole)	0.2 mg (Half)[b]	0.1 mg (Whole)	0.1 mg (Half)
5								
10								
15								
30								
60								

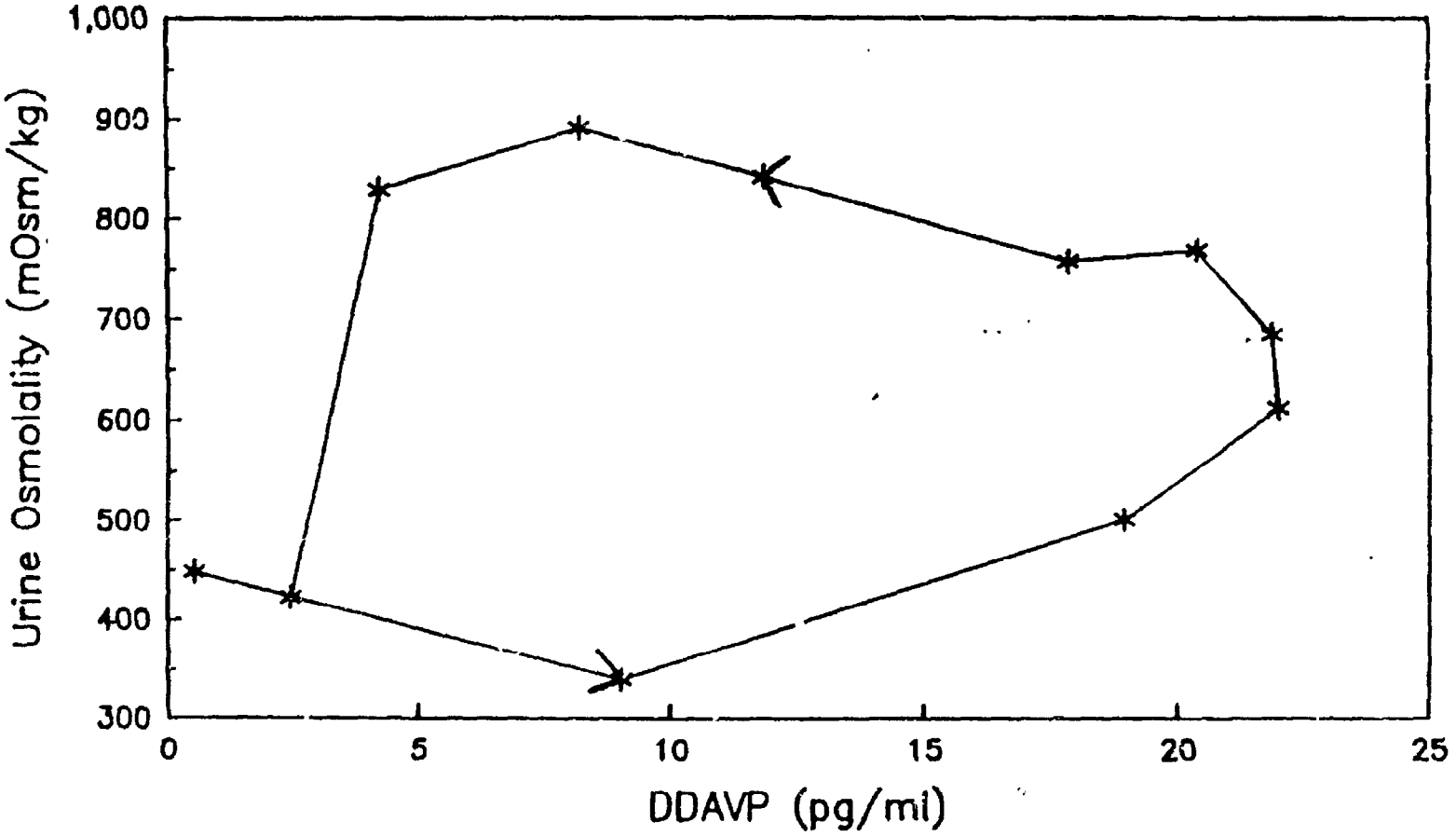
[a]. Batch Nos. of the 0.2 mg and 0.1 mg DDAVP tablets used were QE 9230 and QE 9229, respectively.
[b]. Based on the theoretical amount in each half after broken.
[c]. Standard deviation (SD).

Study 1

FIGURE 6.

RG 84063-101

Urine Osmolality vs DDAVP Concentration for the 0.4 mg DDAVP Dose



Osmolality is Corrected for Baseline
Arrows show the direction of time

TABLE 6 Antidiuretic effect of IN solution of DDAVP after oral administration*

	(n = 5) normal volunteers						(n = 7) Adults with CDI		
	200 μg			100 μg			200 μg		
Time (hr)	UFR[b]	SD	CV (%)	UFR	SD	CV (%)	UFR	SD	CV (%)
0									
1									
2									
3									
4									
5									
6									

*. Information obtained from a published article (Antidiuretic Effect and Pharmacokinetics of Oral DDAVP: Studies in Adults and Children, 1986, by Williams, T., et al., J. Clin. Endocrinol. Met. 63: 129).

[b]. Urine flow rate (ml/hr). All the data including standard deviation were estimated from the graphs.

2 pages
purged